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DEBATES IN THE CAUSAL ASSOCIATION BETWEEN HDL CHOLESTROL AND CV RISK: VIEW POINT FROM RCT AND GENETIC STUDIES

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Abstract

We have long believed that HDL cholesterol is "good" cholesterol. However, failures in recent randomized controlled trials aimed to raise HDL cholesterol as well as findings from Mendelian randomization studies have cast a doubt on its "goodness". Our group has been investigating the associations between blood lipids and cardiovascular (CV) risk among the patients with Mendelian genetic lipid disorders, including familial hypercholesterolemia (FH), sitosterolemia (STL), autosomal recessive hypercholesterolemia (ARH), familial hypobetalipoproteinemia (FHBL), abetalipoproteinemia (ABL), familial hyperchylomicronemia, such as lipoprotein lipase (LPL) deficiency, cholesteryl ester transfer protein (CETP) deficiency, and Tangier disease. Our group has also contributed to Mendelian randomization studies aimed to see the causal association between lipids and CV risk. Those studies have consistently showed us several important facts. 1) genetic variants and diseases associated with LDL cholesterol were associated with CV risk. 2) genetic variants and diseases associated with triglycerides were associated with CV risk. 3) genetic variants and diseases associated with HDL cholesterol were NOT associated with CV risk. On the other hand, we have found that extremely low HDL cholesterol level was significantly associated with several types of fatal situations, including malignancy, and bleeding, not necessarily with CV death. Those observations could lead us to rethink HDL cholesterol as a pure biomarker, not as a causal factor, which we want to increase or decrease. However, functions in HDL particle, such as cholesterol efflux seems to be causally associated with CV risk. Accordingly, we may also need to establish an universal measurement not to quantify, but to qualify our HDL particle.

Keywords

HDL cholesterol; LDL cholesterol; Triglycerides; Cardiovascular genetics